JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 1994, p. 452–456
0095-1137/94/$04.00+0

Vol. 32, No. 2

Genotypic Variation and Slime Production among Blood and Catheter Isolates of *Candida parapsilosis*

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Received 19 August 1993/Returned for modification 3 October 1993/Accepted 9 November 1993

***Candida parapsilosis* is an important nosocomial pathogen that can proliferate in high concentrations of glucose and form biofilms on prosthetic materials. We investigated the genotypic diversity and slime production among 31 isolates of *C. parapsilosis* from individual patients with bloodstream or catheter infections. DNA subtyping was performed by using electrophoretic karyotyping plus restriction endonuclease analysis with *Bss*HII followed by pulsed-field gel electrophoresis. Slime production was evaluated by growing organisms in Sabouraud broth with 8% glucose and examining the walls of the tubes for the presence of an adherent slime layer. Overall there were 14 DNA subtypes among the 31 isolates. Eighty percent of the isolates produced slime; 67% of the isolates were moderately to strongly positive, 13% were weakly positive, and 20% were not slime producers. The ability of isolates of a given DNA type to produce slime under these conditions was variable. The results of these studies indicate moderate genotypic variation among clinical isolates of *C. parapsilosis*. The propensity of these isolates to form slime in glucose-containing solutions suggests that this phenotypic characteristic may contribute to the ability of *C. parapsilosis* to adhere to plastic catheters and cause infections.**

Serious infections with *Candida* species have increased dramatically over the past decade, to the point where *Candida* species have become as common a cause of nosocomial bloodstream infection as several of the gram-negative bacterial pathogens, including *Escherichia coli* and *Pseudomonas aeruginosa* (1, 17). Although *Candida albicans* remains the most common cause of fungemia, there has been an increase in infections due to other *Candida* species including *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. lusitaniae* (11, 17).

C. parapsilosis is well known as a cause of fungemia and invasive candidiasis associated with parenteral hyperalimentation, intravascular devices, and contaminated ophthalmic solutions (15, 16, 18, 19, 22, 23). *C. parapsilosis* is challenging *C. tropicalis* as the second most common cause of fungemia in some institutions and has accounted for 3 to 27% of cases of fungemia in large hospital studies (23). Several factors may give *C. parapsilosis* a selective advantage, including proliferation in high concentrations of glucose and adherence to prosthetic materials (4, 23).

The adherence of *C. parapsilosis* to plastic materials exceeds that of *C. albicans* and is enhanced markedly following growth in a 50 mM glucose solution (4). Although the production of a slime layer (biofilm) in glucose-containing solutions by bacterial pathogens such as *Staphylococcus epidermidis* has been associated with the ability of these organisms to adhere to the surfaces of catheters and other plastic biomedical devices (3, 8), very little information is available regarding similar properties of *C. parapsilosis*. Notably, a report by Marrie and Costerton (14) describes the presence of *C. parapsilosis* in an extensive biofilm on the surface of a catheter obtained from a patient receiving intravenous hyperalimentation, suggesting that these organisms may produce an extracellular substance or slime similar to that observed with *S. epidermidis*.

Despite its importance as an intravascular pathogen, little is known about the pathogenesis and epidemiology of *C. parapsilosis* infection. Much important information about this organism remains to be defined in a systematic fashion, including the genetic diversity among clinical isolates and their abilities to form biofilms (slime) in glucose-containing solutions. Although Carruba et al. (2) and Lott et al. (12) showed that genetic discrimination among isolates of *C. parapsilosis* could be accomplished by electrophoretic karyotype (EK) analysis and suggested that such analysis may offer important clues to the understanding of fungal infection and transmission, these studies have not been extended to involve larger numbers of clinical isolates, including blood and catheter isolates, of *C. parapsilosis*. In the present study we used a simple in vitro test for slime production and DNA typing methods to evaluate slime production and molecular strain variation among blood and catheter isolates of *C. parapsilosis*. The characterization of clinical isolates by DNA subtype and the ability to form slime is a necessary first step in gaining a better understanding of the epidemiology and pathogenesis of *C. parapsilosis* infections.

MATERIALS AND METHODS

Organisms. The test organisms include 31 isolates of *C. parapsilosis* isolated from patients hospitalized at Long Island Jewish Medical Center. The isolates were obtained from blood cultures (18 isolates) or catheter cultures (13 isolates) of individual patients. Only one isolate per patient was included in this study. All isolates were identified as *C. parapsilosis* by standard methods (21).

Molecular typing. Molecular typing of all isolates was

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accomplished by EK analysis and by restriction endonuclease analysis with *Bss*HII and *Sfi*I followed by pulsed-field gel electrophoresis. EK analysis and restriction endonuclease analysis of genomic DNA (REAG) were performed by a modification of the methods of Doebbeling et al. (7). Briefly, 5 to 10 colonies of *C. parapsilosis* grown on Sabouraud agar were inoculated in YEPD broth (1% yeast extract, 2% dextrose, 2% Bacto Peptone) and grown overnight at 30°C in a shaking water bath. The cells were pelleted, and 150 μl of the packed cells was transferred to an Eppendorf tube and washed two times with 200 μl of 50 mM EDTA, pH 8.0. The suspension of cells was evenly mixed with 100 μl of yeast cell wall-degrading enzymes (Lyticase [L5263, partially purified grade], 1,250 U/ml in 50% glycerol [vol/vol]–0.01 M Na PO_4, pH 7.5 [Sigma Chemical Co., St. Louis, Mo.]) and incubated at 37°C for 20 min. Aliquots of 460 μl of 1% low-melting-point agarose (Bio-Rad, Richmond, Calif.) in 125 mM EDTA, pH 7.5, were added to the solution and dispensed into molds to form agarose plugs. The plugs were incubated overnight at 50°C in 1.5 ml of a solution of buffer (0.01 M Tris [pH 7.5], 0.45 M EDTA [pH 8.0], 1% lauroylsarcosine) containing proteinase K (1 mg/ml; protease type XXVIII, 20 U/mg; Sigma). Agarose inserts were washed three times with 3 ml of 50 mM EDTA, pH 8.0, and incubated overnight at room temperature. Washing was repeated two more times on the following day with the same solution. A slice of 1 to 2 mm from the plugs was inserted into a 1% agarose gel, and the chromosome-sized pieces of DNA were resolved with a contour-clamped homogeneous electric field system (CHEF-DR II; Bio-Rad). Electrophoresis was carried out at 150 V and 13°C with pulse intervals of 120 s for 24 h and 240 s for 36 h. After electrophoresis, gels were stained with ethidium bromide and photographed under UV light. *Saccharomyces cerevisiae* chromosome DNA size standards (Bio-Rad) were included in each gel as standards.

For restriction endonuclease digestion, agarose plugs containing chromosome-sized DNA were prepared as described above, and one-third of each plug was placed in 100 μl of buffer containing 20 U of a "low-frequency-cleavage" restriction endonuclease, *Bss*HII or *Sfi*I (New England Biolabs, Beverly, Mass.). Overnight digestion was performed as directed by the endonuclease manufacturer. Contour-clamped homogeneous electric field electrophoresis was performed at 13°C for 24 h at 200 V in a 1% agarose gel (Bio-Rad) with switch times ramped from 5 to 35 s. DNA lambda concatemer markers (Bio-Rad) were placed in both sides of the gels. The gels were stained with ethidium bromide and photographed under UV light.

Analysis of EKs and REAG profiles was performed by visual inspection of photographs of ethidium bromide-stained gels. Each major and minor band was identified, and the distance from the origin of the gel relative to those of the molecular weight standards was measured. Isolates were considered different if any readily detectable band did not match. In order to achieve maximum strain discrimination, the results of the EK analysis and REAG were combined to achieve a composite DNA subtype.

Slime production. Slime production was determined by using a modification of the test described for coagulase-negative staphylococci (3, 5). Briefly, a loopful of organisms from the surface of a Sabouraud dextrose agar plate was inoculated into a tube containing 10 ml of Sabouraud broth supplemented with glucose (final concentration, 8%). The tubes were incubated at 35°C for 24 h, after which they were examined for the presence of a viscid slime layer. Slime production by each isolate was scored as negative, weak (1+), moderate (2+ or 3+), or strong (4+). Each isolate was tested at least five times and read independently by two different observers.

TABLE 1. Molecular sizes of bands characterizing 11 EKs of *C. parapsilosis*

Molecular size (kb)[a]	Presence of band in EK										
	A	B	C	D	E	F	G	H	I	J	K
2,200	X	X	X	X	X	X	X	X	X	X	X
2,100				X							
1,750				X							
1,600	X	X	X		X	X	X	X	X	X	X
1,450				X							
1,380	X	X	X		X	X	X	X	X	X	X
1,300									X		
1,225				X							
1,200	X	X						X			
1,125											X
1,100			X			X	X	X			
1,060			X			X					
1,020	X	X	X		X		X	X	X	X	X
980					X	X					
970		X									
950	X	X	X		X	X	X	X	X	X	X

[a] Apparent molecular sizes determined from comparison with *S. cerevisiae* size standards.

RESULTS

Genetic discrimination among the 31 isolates of *C. parapsilosis* was achieved by EK analysis. EK analysis identified 11 different EKs of *C. parapsilosis* (Tables 1 and 2). Six to eight bands with approximate molecular sizes ranging from 900 to 2,200 kb were identified (Fig. 1 and Table 1). Variations in EK occurred primarily in the middle and lower segments of the gels. Bands of 2,200, 1,600, 1,380, and 950 kb were common to most isolates. Some constituents were not sharply resolved, resulting in a "fuzzy" area of chromosomal DNA (Fig. 1), and these fuzzy areas were present in repeated gels. Overall, 13 of the isolates (42%) were included in EK A (Tables 1 and 2 and Fig. 1). The remaining 18 isolates were in 10 different EKs.

REAG was initially performed with both *Bss*HII and *Sfi*I restriction enzymes. Digestion with *Sfi*I resulted in poor discrimination and will not be discussed further. Restriction

TABLE 2. DNA subtypes of *C. parapsilosis* determined by EK analysis and REAG

EK	No. of isolates of REAG type:				Total no.
	A	B	C	D	
A	9	1	3	0	13
B	1	1	0	0	2
C	2	0	0	0	2
D	0	0	0	1	1
E	0	0	0	1	1
F	1	0	0	0	1
G	5	0	0	0	5
H	1	0	0	0	1
I	2	0	0	0	2
J	2	0	0	0	2
K	1	0	0	0	1
Total	24	2	3	2	31

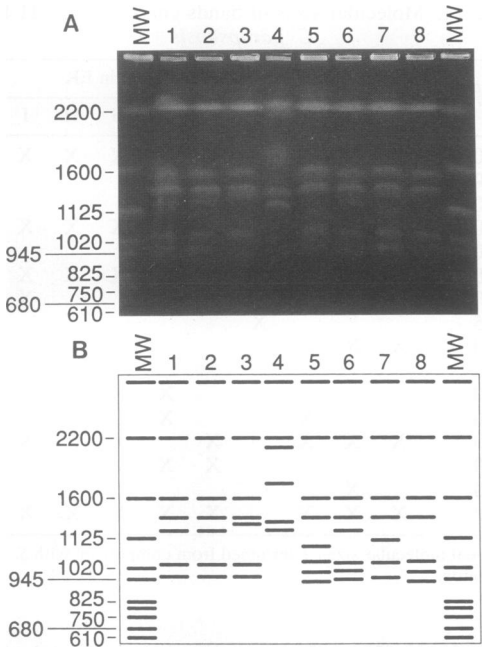

FIG. 1. (A) Representative EK profiles of *C. parapsilosis*. Lanes: MW, *S. cerevisiae* chromosome DNA size standards (in kilobases); 1 and 2, EK A; 3, EK I; 4, EK D; 5, EK F; 6, EK B; 7, EK G; 8, EK E. (B) Schematic diagram of the EK profiles in panel A.

analysis using *Bss*HII followed by pulsed-field electrophoresis generated a large number of fragments and identified four distinct REAG types, A through D (Table 2 and Fig. 2). REAG type A encompassed 24 (77%) of the 31 isolates, whereas REAG types B, C, and D encompassed 2, 3, and 2 isolates, respectively.

The combination of EK analysis and REAG typing results to produce a composite DNA subtype identified a total of 14 different subtypes (Table 2). Although REAG alone identified very few individual types, it did divide the major EK, EK A, into three distinct DNA subtypes, AA, AB, and AC.

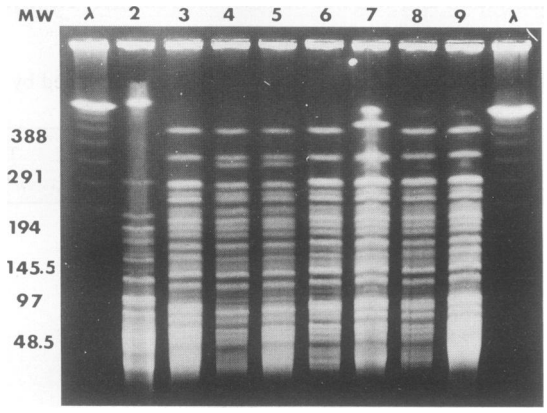

FIG. 2. REAG types of *C. parapsilosis* obtained by using *Bss*HII followed by pulsed-field gel electrophoresis. Lanes: λ, lambda phage DNA concatemers as molecular size standards (in kilobases); 2, REAG type D; 3, 6, 8, and 9, REAG type A; 4 and 5, REAG type B; 7, REAG type C.

TABLE 3. Genotypic variation and slime production among blood and catheter isolates of *C. parapsilosis*

Subtype[a]	No. of isolates	No. with slime production:				
		Strong	Moderate	Weak	Negative	NT[b]
AA	9	0	6	1	2	0
AB	1	0	1	0	0	0
AC	3	0	1	1	0	1
BA	1	0	1	0	0	0
BB	1	0	0	1	0	0
CA	2	0	0	1	1	0
DD	1	0	1	0	0	0
ED	1	0	0	0	1	0
FA	1	0	0	0	1	0
GA	5	0	5	0	0	0
HA	1	0	1	0	0	0
IA	2	0	2	0	0	0
JA	2	1	1	0	0	0
KA	1	0	0	0	1	0
Total	31	1	19	4	6	1

[a] The DNA subtype represents a composite of EK analysis and REAG typing results.
[b] NT, not tested.

Likewise, EK B was divided into two DNA subtypes (BA and BB), and EK D and E were shown to be distinctly different from the remainder of the isolates. Overall, 9 of the isolates (28%) were included in composite DNA subtype AA (Table 2), while the remaining 22 isolates were contained in 13 different composite DNA subtypes.

Slime production was demonstrated in 24 (80%) of 30 *C. parapsilosis* isolates tested (Table 3). One isolate was unavailable for testing. The majority of isolates (67%) were moderately to strongly positive for slime production, four isolates (13%) were weakly positive, and six isolates (20%) were not slime producers. The reproducibility of the slime test was >95%, and in no instance did an isolate switch from strongly or moderately positive to weakly positive or negative or vice versa. The ability of a given DNA subtype to produce slime under these conditions was variable; however, 70% of isolates in subtype AA were moderate slime producers.

DISCUSSION

The results of the present study confirm and extend the findings of Carruba et al. (2), Lott et al. (12), and Vazquez et al. (20) regarding the usefulness of EK analysis in identifying strains or types of *C. parapsilosis*. Carruba et al. (2) identified a total of seven EKs among 16 isolates, with 32% of the isolates included in one EK. Their study included predominantly vaginitis isolates and only four isolates from individuals with candidemia. Three of the four candidemia isolates had the same EK. Vazquez et al. (20) identified a total of 10 EKs among 17 clinical and environmental isolates of *C. parapsilosis*. It was not stated whether any of these isolates were from individuals with candidemia. Two patients shared the same EK, and one patient shared the same EK with environmental isolates. In contrast to the findings of Carruba et al. (2), a predominant EK was not identified. Lott et al. (12) used both EK and randomly amplified polymorphic DNA methods to characterize genetic diversity among isolates of *C. parapsilosis*. They identified several distinct EKs, suggesting a high degree of chromosome-length polymorphisms. They also noted that approximately 70% of the

isolates had similar, but not identical, EK profiles, while the remainder showed pronounced differences. These findings were corroborated by randomly amplified polymorphic DNA PCR analysis. We have shown that EK analysis can identify a considerable number of individual types of *C. parapsilosis* within a collection of clinical blood and catheter isolates from a single institution. The finding of a predominant EK in this collection is not surprising given the findings of Carruba et al. (2) and Lott et al. (12) along with what is known of the epidemiology of *C. parapsilosis* (23), and it suggests the potential of cross-infection among these patients. Further epidemiologic investigation confirming or refuting this hypothesis was not undertaken in this study.

Additionally, we have shown that REAG using low-frequency-cleavage restriction endonucleases, such as *Bss*HII, coupled with pulsed-field electrophoresis using a CHEF-DR II system (Bio-Rad) can provide additional strain discrimination among *C. parapsilosis* isolates. Although the degree of discrimination with REAG was not as great as was observed previously with *C. tropicalis* (7), this approach did allow us to identify subtypes within the major EK group (EK A) in this study. By comparison, the study by Carruba et al. (2) investigated restriction endonuclease analysis of whole genomic DNA and mitochondrial DNA by using high-frequency-cleavage restriction endonucleases (*Eco*RI, *Hin*dIII, *Bam*HI, *Bgl*II, and *Hpa*II) and conventional electrophoresis and found that this approach did not discriminate among isolates in their collection. Similar results with *Eco*RI and *Msp*I were reported by Vazquez et al. (20). This is consistent with our previously unpublished experience with restriction endonuclease analysis of genomic DNA and conventional electrophoresis used to type *C. parapsilosis* (data not shown). The usefulness of the composite typing approach with EK analysis plus REAG typing for *C. parapsilosis* remains to be seen in future epidemiological studies.

The in vitro demonstration of slime production in isolates of coagulase-negative staphylococci has been used as both an epidemiologic marker and a means of discriminating among pathogenic and contaminating isolates from blood cultures (5, 6, 10). Although the clinical value of a test for slime production is controversial, data from several studies suggest that isolates that produce copious amounts of slime in glucose-containing solutions are more likely to represent clinically significant infection and may be more difficult to eradicate with antibiotic therapy than those that are slime negative (5, 6). In particular, slime production by coagulase-negative staphylococci has been associated with the ability of these organisms to adhere to the surfaces of catheters and other plastic biomedical devices (3, 8). Despite the importance of *C. parapsilosis* in vascular device-related infections, there has been little or no investigation of the ability of this organism to produce a biofilm or slime-like substance. The use of scanning electron microscopy to study catheters and valve material from patients with endocarditis suggests that the organism is capable of forming biofilms in vivo (13, 14). Although very preliminary, the present study provides some in vitro evidence that the majority of *C. parapsilosis* isolates from blood and catheter cultures have the capability of producing large amounts of viscid slime material in glucose-containing solutions. This phenotypic trait is not shared by all members of a given DNA subtype. Clearly some strains produce more slime than others under these conditions. The lack of correlation between slime production and DNA type in *C. parapsilosis* is not surprising, given similar findings with coagulase-negative staphylococci (9). It appears that phenotypes related to pathogenicity may assort independently from gross chromosomal restructuring as determined by EK analysis. This may reflect a fundamental restriction on the usefulness of karyotyping in such analyses. The clinical implications of these preliminary observations are unclear, and additional studies are certainly warranted. The use of a phenotypic marker, such as slime production, in combination with DNA subtyping may prove to be a useful means of typing *C. parapsilosis* for epidemiologic purposes.

In summary, the results of these studies indicate considerable genotypic variation among clinical isolates of *C. parapsilosis*. The use of EK analysis and REAG typing to produce a composite DNA subtype provides a means of genetic discrimination among *C. parapsilosis* isolates and should facilitate future epidemiological studies. The propensity of *C. parapsilosis* isolates to form slime in glucose-containing solutions suggests that this phenotypic characteristic may contribute to the ability of *C. parapsilosis* to adhere to plastic catheters and cause infections in individuals receiving intravenous hyperalimentation. Additional studies of the epidemiology and pathogenesis of *C. parapsilosis* infections are clearly indicated.

ACKNOWLEDGMENTS

We acknowledge the excellent secretarial support of Bea Dacy and Kay Meyer.

This work was supported in part by Pfizer Pharmaceuticals-Roerig Division. M. L. Branchini is a visiting research scientist in the Department of Pathology, Oregon Health Sciences University, and is supported by grant 91/2937-9 from Fundacao de Amparo a Pesquisa do Estado de Sao Paulo and Universidade Estadual de Campinas, Sao Paulo, Brazil.

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